not share the same aim at all, even if one defines the skilled person as an expert in the neurodegenerative diseases art. PRATT does not relate to the resolution of the same problem as the present invention, nor does it contain any mention of the treatment of cerebral ischemia.

The focal photothrombotic model used by PRATT is not suitable for provoking a neurological deficit in the rat. A Pub-Med database search shows no publications on neurological deficits after photothrombotic cortical injury. Using 'behavioral deficit' did not yield other references.[1] This is further support for Applicants' position that the photothrombotic test used in the cited publication by PRATT, does not present visible symptoms of loss of function, as associated with stroke in man.

Morever the present application is directed to the use of enoxaparin in the treatment of cerebral ischemia. The action of enoxaparin is linked to a diminution of the cortical lesion and an improvement of the neurologic score of the animals (initially disturbed by the ischemic process). The brains lesions induced by the PRATT experiment and the lesions induced in the experiments of the present application are different. In PRATT, they are much less prominent, less deep, appear more rapidly, with a different localization; the lesions are focused at the zone where the photothrombotic insult is applied. The model described in PRATT to induce brain lesions is less intense than the one described in the present patent application.Indeed, reperfusion injury is a major factor in stroke damage (Deitrich, 1994) not addressed by PRATT and not covered in the photothrombotic model described by these workers. Thus, there is no evidence of reperfusion in the PRATT model. As such, this model is of less relevance to stroke than are the models of middle cerebral artery occlusion.

WO 01/49298 A2 discloses the use of models of both reversible and irreversible cerebral ischemia to demonstrate Enoxaparin's efficacy (see Clark et al., 1994 for comparison of models). In the irreversible model, the middle cerebral artery is cauterized, provoking a cerebral ischemia without reperfusion. In the reversible model, the left middle cerebral artery is clipped for 2 hours, then the clip is removed, and the brain is reperfused. This will provoke an extensive reperfusion injury. Reperfusion injury is considered to be a major factor in thromboembolic stroke, where a thrombus may break up or move further up a vessel, whereby affected parts of the brain, behind a compromised blood/brain barrier are reconnected to the blood supply. Inflammation is seen (Kogure et al, 1995) and toxic materials (lysed cell contents, hemoglobin from erythrocytes, cytokines, neurotransmitters, etc) are transported into the surrounding tissue, while there is neutrophil infiltration (Adachi et al, 2004), and plasma proteins etc gain access through the vessel walls to the parenchyma. The reappearance of oxygen in ischemic tissues also provokes an oxidative stress, upon which Enoxaparin might act. PRATT does not monitor reperfusion in his publication, and there is no information about reperfusion after photothrombotic injury; but it can be assumed that if, all the vessels in an area of brain have been blocked by photothrombosis, then no reperfusion takes

place, oxygen levels remain very low and the protective role of enoxaparin in reperfusion injury, a major component of stroke, could not be evaluated.

Thus, the cited references do not support the Examiner's argument that the PRATT reference discloses performing the recited step on the required subject, thereby accomplishing the claimed method. Indeed, in view of the above arguments, it can be seen that there were no a significant lesions in the PRATT model that could allow an induction of functional deficit and thus an action of enoxaparin to treat cerebral ischemia. PRATT can not accomplishing the method of the present patent application since PRATT does not disclose the required subject on which enoxaparin can act. Accordingly, the cited PRATT reference does not describe nor suggest the use of enoxaparin in the treatment of cerebral ischemia.

PRATT investigates the effect of enoxaparin on oedema following a photothrombic injury in the rat. While cerebral oedema can be one of the consequences of cerebral ischemia, there is not necessarily a direct link between cerebral ischemia and cerebral oedema. For example, oedema can more or less be reabsorbed without any reduction in the ischemic area. There are examples in the literature which demonstrate that neuroprotection and brain edema are not synonymous. This is the case for dizocilpine (MK-801) which was shown to reduce brain edema (McIntosh et al., 1990) but was not able to reduce the brain lesions (Toulmond et al., 1993). In another study, aminoguanidine was shown to reduce the brain lesions without any reduction of the brain edema (Zhang et al. 1996). Therefore, brain edema reduction can be independent of neuroprotection, and vice versa. As a result, the fact that a compound, like enoxaparin, may be useful in the reduction of oedema does not necessarily imply that the same compound will have antiischemic action. In view of the above, the description in PRATT that enoxaparin may be used to treat cerebral oedema is not equivalent to a disclosure of a method in which enoxaparin can be used to treat cerebral ischemia. For this reason, too, PRATT does not anticipate the subject matter of claim 1.

The action of enoxaparin is linked to a diminution of the cortical lesion and an improvement in the neurological score of animals, initially disturbed by the ischemic process. However, Pratt et al. is entirely silent about anti-ischemic action and about reduction in lesion size and, hence, would not prompt the skilled person in the art to consider using enoxaparin for this application. In addition, the Examiner admits that the Pratt et al. reference does not disclose reduction in lesion size.

[1]References:

Copies of the following references, discussed herein, are submitted herewith together with a Supplemental Information Disclosure Statement:

Adachi N, Liu K, Arai T. Alleviation of ischemic neuronal damage by postischemic loading with histidine in the rat striatum. Brain Res. 2004 Feb 13;998(1):136-8.

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Dietrich WD. Morphological manifestations of reperfusion injury in brain.Ann N Y Acad Sci. 1994 Jun 17;723:15-24.

Kogure K, Yamasaki Y, Matsuo Y, Kato H, Onodera H. Inflammation of the brain after ischemia. Acta Neurochir Suppl (Wien). 1996;66:40-3

McIntosh T K., Journal of Neurochemistry, Vol. 55, No 4, 1990.

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